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Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study

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Summary

Objective: To examine the efficacy and safety of two doses of long-acting acetaminophen in patients with osteoarthritis (OA) of the hip or knee.

Methods: This multicenter, randomized, double-blind, parallel-group, placebo-controlled study evaluated the efficacy and safety of acetaminophen extended-release (ER) 650 mg and 1300 mg given three times daily for the treatment of moderate to moderately severe OA of the hip or knee. Primary efficacy end points were mean change from baseline through 12 weeks in the Western Ontario and McMaster Universities Osteoarthritis Index pain and physical function subscale scores and mean patient global assessment of response to therapy at week 12. Safety assessments included monitoring vital signs, adverse events, study joint assessments, and clinical laboratory results at each study visit.

Results: Four hundred eighty-three patients were randomized to treatment and included in the intent-to-treat analysis. All groups were similar with respect to baseline demographics except for gender, weight, and body mass index. Acetaminophen ER 3900 mg was significantly superior to placebo for all three primary end points; acetaminophen ER 1950 mg was significantly superior to placebo only with respect to patient assessment of response to therapy. Study treatments were generally well tolerated, and there was no significant difference among the groups in the overall number of adverse events.

Conclusions: Acetaminophen ER 3900 mg/d administered for up to 12 weeks was effective in treating moderate to moderately severe chronic OA pain of the hip or knee and was generally well tolerated.

Key words: Acetaminophen, Efficacy, Hip, Knee, Osteoarthritis, Pain.

Introduction

Osteoarthritis (OA) is a rheumatic disease characterized by articular cartilage degeneration, bone hypertrophy, crepitus, and radiographic changes that is estimated to affect nearly 20% of Americans[1,2]. The joint pain and stiffness associated with OA can lead to significant disability and functional impairment. Among the elderly, OA of the knee is the leading cause of chronic disability; an estimated 100,000 people in the United States are unable to walk independently from bed to bathroom because of knee or hip OA[3]. Therefore, controlling these symptoms is critically important to treatment.

The cost of illness resulting from direct expenditures for medical care services associated with OA and/or costs resulting from the indirect impact of illness on function are substantial. In 1992, total direct and indirect costs associated with treatment of arthritis in the United States were $64.8 billion; $15.2 billion for medical costs, and $49.6 billion for costs that resulted from lost productivity[4]. Since half of these patients have clinically diagnosed OA, these expenditures are considerable and consistent with other estimates[2,5–7].

Acetaminophen extended-release (ER) is a long-acting analgesic and antipyretic medication indicated for the temporary relief of minor aches and pains caused by arthritis, the common cold, headache, toothache, muscular aches, backache, and menstrual cramps[8]. Acetaminophen ER caplets contain acetaminophen 650 mg in a bilayer form that has both immediate-release (IR) and ER components. In various studies[9–11], acetaminophen has been shown to be comparable to nonsteroidal antiinflammatory drug (NSAID) treatments for the relief of mild to moderate joint pain associated with OA. However, limited data from well-designed, placebo-controlled studies are available.

This 12-week study was conducted to evaluate the efficacy and safety of two doses of a formulation of acetaminophen not previously evaluated: acetaminophen ER 650 mg and 1300 mg administered three times a day compared with placebo for the treatment of moderate to moderately severe pain associated with OA of the hip or knee. Based on the authors' clinical experience, OA patients are not always compliant with acetaminophen dosed four times daily, which may lead to inadequate therapeutic response. The purpose of this acetaminophen formulation is to reduce the number of daily doses required to achieve the maximum therapeutic dose of acetaminophen. It is expected that dosing three times daily will improve

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compliance and allow the therapeutic program to reach the maximum effective dose.

Methods

PATIENT POPULATION

Four hundred eighty-three patients 40 years of age or older who experienced at least moderate pain when not taking any analgesic medication for OA of the hip or knee were enrolled in this study. Clinical inclusion criteria were the presence of symptomatic idiopathic OA of the hip or knee for a minimum of 6 months with a history of hip or knee pain requiring the use of NSAIDs, acetaminophen, or other analgesic agent on a regular basis (3 or more days per week) for at least 3 months before the screening visit. Patients must also have had a history of positive therapeutic benefit with acetaminophen use for OA pain. This study was conducted to evaluate the efficacy of a formulation of acetaminophen not previously evaluated in hip or knee OA. The requirement of a response to acetaminophen was felt to be appropriate in this setting and is analogous to the ''flare'' design used in most trials of antiinflammatory agents. In addition, patients must have reported maximum OA pain intensity experienced during the 24 h prior to the baseline visit at a pain level of moderate (2) or moderately severe (3) on a 5-point Likert scale defined as none (0), mild (1), moderate (2), moderately severe (3), or severe (4). If qualifying with OA of the knee, patients had to have knee pain and radiographic osteophytes, and fulfilled at least one of the following three criteria: experienced morning stiffness of less than 30 min of duration, experienced crepitus on motion, or been at least 40 years of age[12]. If qualifying with OA of the hip, patients must have had hip pain, radiographic femoral and/or acetabular osteophytes, and radiographic joint-space narrowing as established by the American College of Rheumatology (ACR) criteria for idiopathic OA of the hip[13]. Patients must also have demonstrated an increase in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score of at least 20% relative to the screening visit score. All women of childbearing potential were required to have a negative urine pregnancy test and used an effective method of birth control during the study.

A patient was excluded from the study if there was a history of surgery or major trauma to the study joint in the 6 months prior to the screening visit. Patients taking analgesic therapy for other indications, or those taking anticoagulants, psychotherapeutic agents, aspirin in daily doses greater than 325 mg, or statin-class hypolipidemic agents in doses that had not been stabilized within 3 months of the screening visit were also excluded. In addition, patients taking glucosamine, chondroitin sulfate, or shark cartilage in doses that had not been stabilized within 6 months of the screening visit, and those with known alcohol abuse, intravenous drug use, drug dependency, or history of significant psychiatric illness in the previous 12 months were excluded. Administration of oral corticosteroids within 2 months of screening or intraarticular or periarticular corticosteroid or hyaluronan injections into the study joint within 6 months of screening were prohibited. Other exclusion criteria were history of gastrointestinal or hepatic disease[14], clinically apparent inflammation of the study knee joint, secondary OA of the study joint, history of acute inflammatory arthritis or pseudogout of the study joint, or medical history, physical examination, or radiographic evidence suggestive of other types of arthritis, collagen vascular disease, or fibromyalgia.

This study was conducted at 47 investigational sites in the United States between 17 April 2002 and 27 March 2003. The study was approved by the institutional review board at each study center, and written informed consent was obtained from each patient before entry into the study. The study was conducted under the guidance of Good Clinical Practice.

STUDY DESIGN

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study consisting of a screening visit, a washout period during which use of all prestudy OA pain medications was not permitted within five drug half-lives of the baseline visit, a randomization visit corresponding to baseline (with treatment allocation), and four study visits while the assigned study medication was being administered (at weeks 2, 4, 8, and 12). During the washout period, patients could not take any prescription or over-the-counter NSAID, acetaminophen, aspirin, or analgesic in any form. Patients who had pain during the washout period were permitted to take acetaminophen as rescue analgesia up to 24 h before the baseline visit. In addition, telephone contact was performed at weeks 1, 3, 5, 6, 7, 9, 10, and 11 to review all pertinent study issues, including compliance with dosing of study medication and use of rescue medication.

Patient eligibility requirements at the screening visit were a serum alkaline phosphatase (ALP) value less than or equal to 1.5 times the upper limit of the reference range (ULRR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and blood urea nitrogen (BUN) values less than or equal to 1.25 times the ULRR, a rheumatoid factor that was negative or less than 40 IU/mL, serum creatinine level less than or equal to 1.5 mg/dL, and remaining laboratory values within normal range. Following the screening visit, all qualifying patients underwent a washout period from their usual OA pain medications.

Patients attended a screening visit to verify eligibility and to undergo study evaluation. OA history and disease condition were documented by asking the patient, ''How would you describe your history of OA pain when not taking analgesic medications?'' Response was based on a 5-point Likert scale ranging from none (0) to severe (4). The study knee joint was assessed for redness, warmth, and effusion, and the study hip joint for crepitus, restricted range of motion, and tenderness. Physical ability was categorized as ACR functional class I, II, or III[12,13]. The diagnosis of OA based on Kellgren and Lawrence radiographic entrance criteria of grade 2 or 3 OA[15] was confirmed by review of a recent (within the previous 6 months) weight-bearing, anteroposterior radiograph of the symptomatic knee joint or nonweight-bearing anteroposterior radiograph of the symptomatic hip joint.

Qualified patients were randomly assigned to one of three treatment groups. One group received acetaminophen ER 1950 mg daily in three divided doses, another group received acetaminophen ER 3900 mg daily in three divided doses, and the third group received placebo in three divided doses. Patients were instructed to take the assigned study medication every 8 h for 12 weeks or until study discontinuation. Patients were guided on the appropriate use of self-administered nonpharmacologic therapies for breakthrough OA pain, and if pain relief was inadequate, propoxyphene HCl (maximum dose, 390 mg/d) was permitted as the only rescue analgesic medication and was to be used for no more than 3 days in any 7-day period. Patients were not

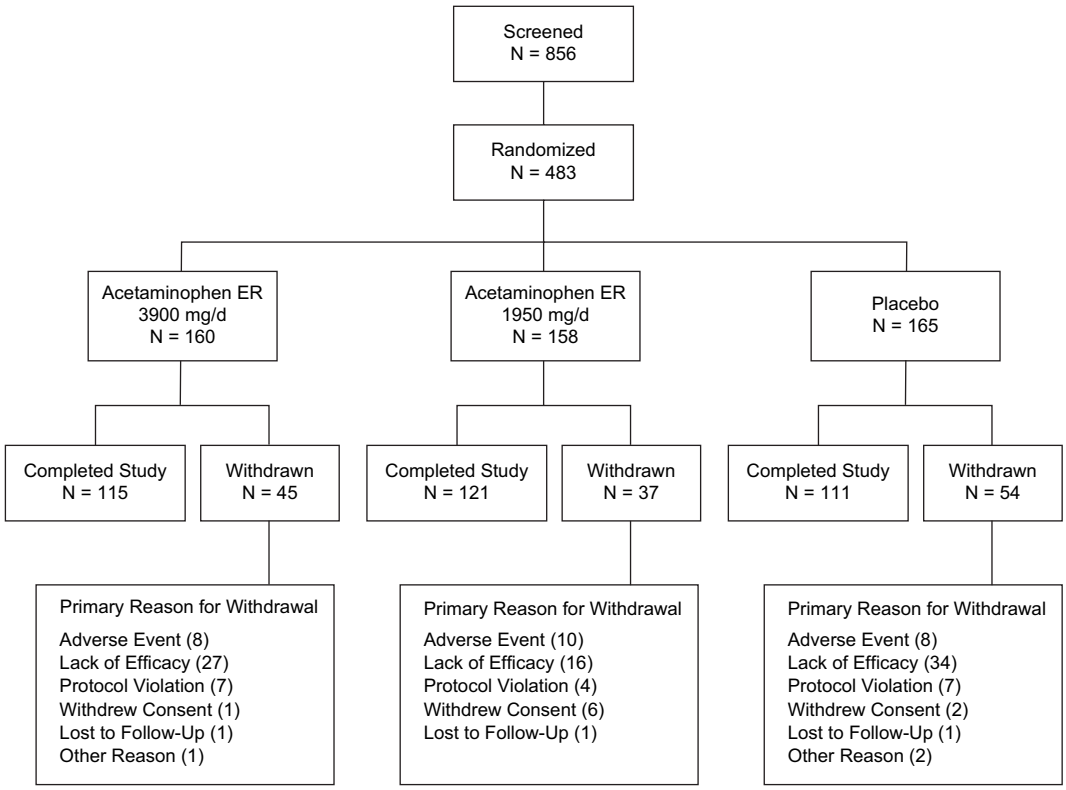

Fig. 1. Patient disposition.

permitted to use rescue or other prescription analgesic medications within five drug half-lives before follow-up visits for efficacy assessments.

Patients attended visits at the end of weeks 2, 4, 8, and 12, or upon early discontinuation from the study. At each visit, the visual analog scale (VAS) version of the WOMAC, laboratory evaluations, vital signs recording, patient global assessment of response to therapy, and study joint assessments were performed. Patients assessed response to therapy by answering the question, ''Considering the overall effects of the study medication on your OA symptoms, how would you rate your response to therapy today?'' using a 5-point scale of 0 (none − no good at all, ineffective), 1 (poor − some effect, but unsatisfactory), 2 (fair − reasonable effect, but could be better), 3 (good − satisfactory effect with occasional episodes of pain and/or stiffness), or 4 (excellent − ideal response, virtually pain free). Patients were instructed to bring all used and unused study medication blister cards and containers of propoxyphene HCl at each visit to assess compliance and use of rescue

Table I
Baseline demographic characteristics for the ITT population

Characteristic	Acetaminophen ER 3900 mg/d ($N = 160$)	Acetaminophen ER 1950 mg/d ($N = 158$)	Placebo ($N = 165$)	Total ($N = 483$)
Gender (%)				
Female:male ratio	71.3:28.8	57.6:42.4	71.5:28.5	66.9:33.1*
Mean age, y (SD)	61.7 (10.7)	63.1 (10.9)	61.8 (10.7)	62.2 (10.8)
Range	40–85	40–90	40–84	40–90
Mean weight, lb (SD)	208.2 (60.7)	193.6 (44.6)	202.7 (49.4)	201.6* (52.2)
Range	112–450	95–400	101–378	95–450
Mean screening height, in (SD)	65.5 (4.1)	66.4 (4.0)	65.5 (4.2)	65.8 (4.1)
Range	56–78	56.5–77	52–80	52–80
Mean body mass index, kg (SD)	34.1 (9.3)	30.8 (6.2)	33.2 (7.9)	32.7*
Median	31.7	29.9	31.8	31.0
Range	19.4–66.4	17.4–55.1	19.7–60.6	17.4–66.4
Race (%)				
Caucasian	81.3	84.8	80.0	82.0
African American	10.0	4.4	11.5	8.7
Other	8.8	10.8	8.5	9.3

SD = standard deviation. *$P < 0.05$.

Table II
Baseline disease characteristics for the ITT population

Characteristic	Acetaminophen ER 3900 mg/d ($N = 160$)	Acetaminophen ER 1950 mg/d ($N = 158$)	Placebo ($N = 165$)
OA site			
Knee	130	128	135
Hip	30	30	30
Patient's assessment of OA pain (%)			
Moderate	26.9	23.4	21.2
Moderately severe	73.1	76.6	78.8
Redness of knee joint (%)			
Absent	100	100	100
Knee joint warmth (%)			
Absent	100	100	100
Knee effusion (%)			
Absent	100	100	100
Hip joint restricted range of motion (%)			
Absent	100	100	100

analgesia; study staff counted and documented the number of used and unused caplets of study medication and the number of used propoxyphene HCl capsules at each visit.

EFFICACY ASSESSMENT

Primary efficacy end points were mean change from baseline through week 12 (or final on-therapy visit) for WOMAC pain and WOMAC physical function subscale scores and mean patient global assessment of response to therapy through week 12 (or final on-therapy visit). Secondary efficacy end points were mean change from baseline through week 12 (or final on-therapy visit) for WOMAC stiffness subscale score and WOMAC total index, and mean number of rescue medication capsules taken each day while participating in the study. Safety assessments consisted of monitoring vital signs, adverse events, study joint assessments, and clinical laboratory determinations at each visit.

TREATMENT ALLOCATION

Of the 483 patients eligible for randomization, 160 patients were assigned to acetaminophen ER 3900 mg/d (2×650-mg acetaminophen ER caplets administered orally every 8 h; McNeil Consumer Products Co, Fort Washington, PA), 158 patients were assigned to acetaminophen ER 1950 mg/d (1×650-mg acetaminophen ER caplet plus one placebo caplet administered orally every 8 h), and 165 were assigned to receive placebo (two placebo caplets administered orally every 8 h). The placebo caplets were supplied by a McNeil-designated contractor and were similar in color, size, and shape to the acetaminophen ER caplets.

STATISTICAL ANALYSES

A sample size of 155 patients per treatment group was needed to ensure 90% power to detect a difference means of 10 mm on the WOMAC pain domain VAS assuming a standard deviation of 27 using a two group t test with a 0.05 two-sided significance level.

Analysis of primary and secondary efficacy end points was based on the intent-to-treat (ITT) population, which included all randomized patients; data from specific visits were excluded when (1) the visit occurred at least 1 day after discontinuation from the study, or (2) when a visit occurred after (a) the patient used propoxyphene HCl and/or another rescue medication indicated for OA pain for more than 3 days in any 7 day period, (b) the patient took more than six propoxyphene HCl caplets in any single calendar day, or (c) the patient received intraarticular or periarticular corticosteroid or hyaluronan injections of the study joint during the 12 week study period. Safety analysis was conducted on all randomized patients who took at least one dose of study medication. In this study, the ITT and safety populations were identical.

Analysis of covariance (ANCOVA) models with treatment and investigator as fixed effects and the corresponding baseline value as a covariate were used to analyze mean

Table III
Average change from baseline values for the primary and secondary efficacy outcome measures in the ITT population

End point		Acetaminophen ER 3900 mg/d ($N = 160$)	Acetaminophen ER 1950 mg/d ($N = 158$)	Placebo ($N = 165$)
Mean WOMAC pain subscale score (SD)	Baseline	68.9 (19.7)	67.9 (16.5)	66.3 (19.3)
	Treatment period	42.4 (24.8)	45.1 (22.7)	46.7 (25.8)
	Average change from baseline	−26.5 (25.5)	−22.8 (21.6)	−19.6 (22.5)
Mean WOMAC physical function subscale score (SD)	Baseline	69.1 (18.3)	65.9 (18.9)	65.3 (19.4) ($N = 164$)
	Treatment period	44.2 (25.1)	47.1 (24.9)	47.5 (25.8)
	Average change from baseline	−24.9 (24.6)	−18.8 (21.9)	−17.8 (22.3)
Mean WOMAC stiffness subscale score (SD)	Baseline	69.8 (20.9) ($N = 148$)	67.3 (18.8) ($N = 150$)	69.5 (19.6) ($N = 145$)
	Treatment period	44.5 (24.3)	47.1 (24.6)	48.9 (25.7)
	Average change from baseline	−25.3 (27.3)	−20.2 (24.0)	−20.6 (24.8)
Mean WOMAC total index score (SD)	Baseline	69.1 (18.1)	66.5 (17.4)	65.8 (18.6) ($N = 164$)
	Treatment period	44.0 (24.8)	46.8 (24.0)	47.5 (25.3)
	Average change from baseline	−25.1 (24.5)	−19.7 (21.2)	−18.2 (22.0)

All WOMAC subscale scores were normalized to a scale of 0 to 100.

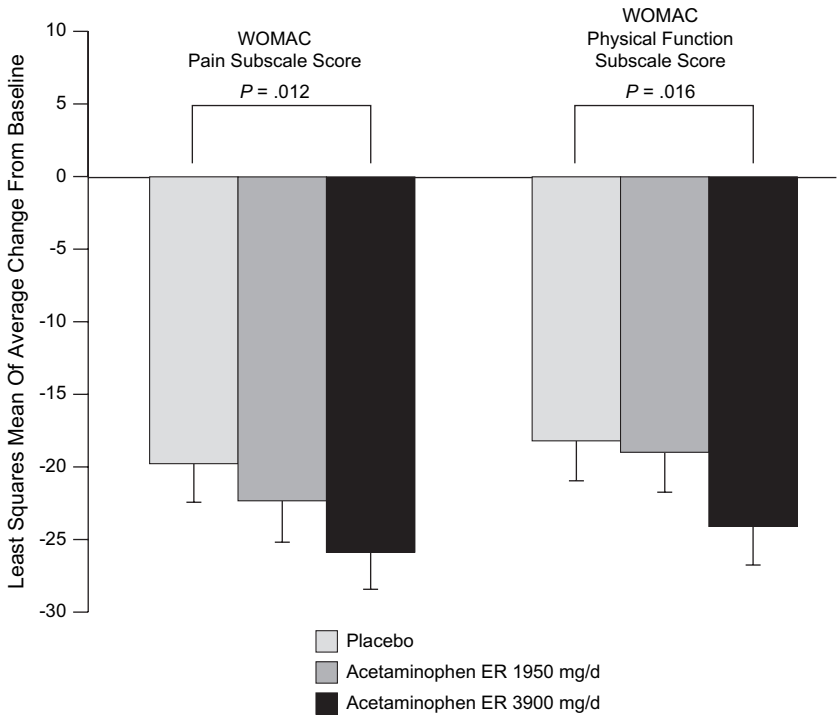

Fig. 2. Mean change from baseline through week 12 for WOMAC pain and physical function subscale scores. For WOMAC pain, the treatment-by-baseline pain term is included in the model; pairwise comparisons are made at the average value of baseline pain (67.68).

change from baseline through week 12 (or final on-therapy visit) in WOMAC pain subscale, physical function subscale, stiffness subscale, and total index. The average subject's assessment of response to therapy was analyzed using an ANCOVA model with treatment and investigator as fixed effects and the WOMAC pain subscale score at baseline as a covariate; if the covariate term was not significant, it was dropped from the model. The treatment-by-investigator and treatment-by-covariate interactions were also evaluated. If the *P* value for the interaction term(s) was greater than 0.10, the interaction term(s) was not included in the final model. Statistical comparisons of the two active treatment groups with placebo were made with respect to least squares means. The least squares mean adjusts for factors in the statistical model such as site variation and baseline covariates. No statistical comparisons were made between the two active treatment groups because the purpose of the study was to determine the effective dose compared with placebo. For the primary efficacy variables, study joint and the interaction term of treatment-by-study joint were introduced into the statistical models to determine if treatment behaves differently depending on the study joint.

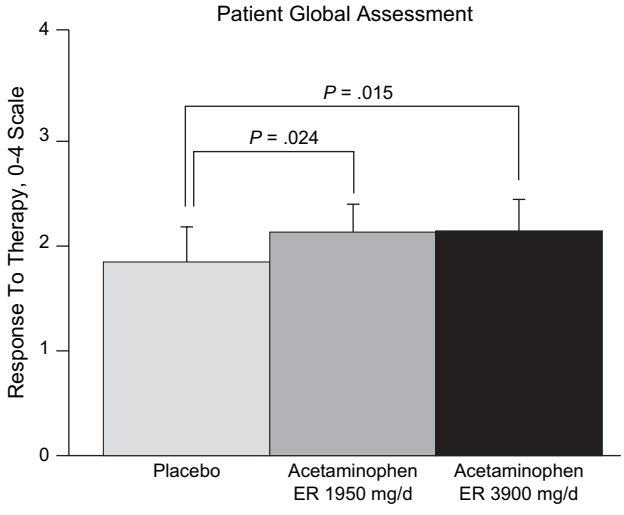

Fig. 3. Mean patient global assessment through week 12.

Comparability among treatment group demographics was assessed using one-way analysis of variance (ANOVA) for continuous variables (age, weight, height, body mass index [BMI]) and Chi-square tests for categorical variables (race, sex, baseline clinical measures). The mean number of rescue medication capsules taken per day was analyzed using an ANOVA model, with treatment and investigator as fixed effects. Fisher's exact test was used to analyze comparisons of adverse events, the proportion of patients using more than the allowed amount of rescue medication, and the proportion of patients discontinuing the study because of a lack of efficacy.

Results

BASELINE CHARACTERISTICS

Eight hundred fifty-six patients were screened, 483 of whom met clinical inclusion criteria and were randomized to treatment; 347 (72%) patients completed the study (Fig. 1). Baseline characteristics of the patients included in the ITT population are summarized in Tables I and II. All groups were similar with the exception of a statistically

Table IV
Least squares means of average change from baseline through week 12 for WOMAC scores in the ITT population

End point	Acetaminophen ER 3900 mg/d ($N = 160$)	Acetaminophen ER 1950 mg/d ($N = 158$)	Placebo ($N = 165$)	*P* value*
WOMAC pain subscale score†	−25.9 (1.76)	−22.5 (1.77)	−19.8 (1.74)	0.012
WOMAC physical function subscale score†	−24.2 (1.80)	−19.0 (1.80)	−18.2 (1.77) ($N = 164$)	0.016
WOMAC stiffness subscale score†	−25.2 (2.0) ($N = 148$)	−21.1 (2.0) ($N = 150$)	−20.5 (2.0) ($N = 145$)	0.088
WOMAC total index score†	−24.5 (1.8)	−19.8 (1.8)	−18.6 (1.8) ($N = 164$)	0.015

*Acetaminophen 3900 mg/d vs placebo.
†Least squares mean change from baseline (standard error).

significant difference among treatment groups with respect to male:female ratio ($P = 0.0104$), baseline weight ($P = 0.0421$), and BMI ($P = 0.0008$). Specifically, the percentage of women, the mean body weight, and the mean BMI were lower in the acetaminophen ER 1950-mg/d group than in the other two groups. Overall, the mean age of the study population was 62.2 years, and the study population was mainly women (67%) and Caucasian (82%). Approximately 75% of the patients in each treatment group had moderately severe OA pain. Thirty patients in each treatment group had hip OA; the remaining 393 patients had knee OA. Baseline values for primary and secondary efficacy outcome measures for all three treatment groups are shown in Table III.

EFFICACY RESULTS

Acetaminophen ER 3900 mg/d was superior to placebo for all three primary end points, as indicated by a significantly greater mean change from baseline in WOMAC pain subscale score, WOMAC physical function subscale score (Fig. 2), and patient global assessment (Fig. 3). Improvements in WOMAC pain subscale score, WOMAC physical function subscale score, and patient global response were statistically superior ($P < 0.05$) for acetaminophen 3900 mg/d compared with placebo from weeks 4 through 12. In the analysis of the WOMAC pain subscale, the significance level ($P = 0.0685$) of the baseline pain–treatment interaction term implies that the 3900-mg/d treatment may perform better at higher levels of baseline pain. As baseline pain increases, the change from baseline also increases, with the regression lines crossing at a baseline pain score of approximately 45. Acetaminophen ER 1950 mg/d was significantly superior to placebo with respect to one primary end point of patient's global assessment of response to therapy, with the difference noted as early as week 4 ($P < 0.05$). Primary efficacy results did not differ between hip or knee based on ANCOVA analyses. No analysis was conducted to assess effects by gender.

In the secondary efficacy analyses, the mean change from baseline for WOMAC total index in the acetaminophen ER 3900-mg/d group was significantly greater than in the placebo group (Table IV); significant changes were noted at each time point after week 2 ($P < 0.05$). No other statistically significant differences among treatment groups were noted for secondary end points. There was no significant difference among treatment groups in the mean number of capsules of rescue medications used.

The overall rate of withdrawal from the study was slightly higher in the placebo group (32.7%) than in the acetaminophen ER groups (28.1% for the 3900-mg/d group and 23.4% for the 1950-mg/d group). The most frequent primary reason for discontinuation in all treatment groups was lack of efficacy, which was reported at a higher rate in the placebo group (20.6% of patients) than in the acetaminophen ER groups (16.9% for the 3900-mg/d group and 10.1% for the 1950-mg/d group) (Fig. 1).

Table V
Number and percent of patients with the most commonly reported (≥5% in any one treatment group) adverse events

Preferred term	Acetaminophen ER 3900 mg/d ($N = 160$) *n* (%)	Acetaminophen ER 1950 mg/d (N = 158) *n* (%)	Placebo ($N = 165$) *n* (%)	*P* value*
Headache	9 (5.6)	7 (4.4)	5 (3.0)	0.502
Infection	9 (5.6)	6 (3.8)	9 (5.5)	0.752
Pain	8 (5.0)	13 (8.2)	8 (4.8)	0.394
Diarrhea	9 (5.6)	7 (4.4)	4 (2.4)	0.331

**P* value based on Fisher's exact test. N = total number of patients in safety population within a treatment group; n = number of patients reporting an adverse event.

ADVERSE EVENTS

There were no significant differences among the groups in the percentage of subjects with adverse events reported or the percentage of patients with serious adverse events. Overall, 44.4% of patients in the acetaminophen ER 3900-mg/d group, 44.9% of patients in the acetaminophen ER 1950-mg/d group, and 40.0% of patients in the placebo group reported one or more adverse events. The number and percent of patients with commonly reported adverse events (at least 5% of patients in any one treatment group) by treatment group are summarized in Table V. Adverse events considered by physicians to be related to treatment were reported by 8.1% of patients in the acetaminophen ER 3900-mg/d group, 9.5% of patients in the acetaminophen ER 1950-mg/d group, and 4.8% of patients in the placebo group ($P = 0.25$). Overall, eight patients reported serious adverse events (three each in the acetaminophen ER 3900-mg/d and 1950-mg/d groups and two in the placebo group); none of the adverse events were considered to be drug related. There was one death in the study (a patient treated with placebo) as a result of an auto accident; the death was not considered to be drug related.

Three patients (1.9%) in the acetaminophen ER 3900-mg/d group had either AST and/or ALT levels greater than three times the ULRR. In two of these three patients,

comorbid diseases or concomitant medications administered could have caused elevations in liver function tests. Liver function tests returned to normal in one of the two who continued treatment and in the other patient after discontinuation of acetaminophen ER. No specific causative factors were identified in the third patient, however; liver function tests returned toward normal while the patient remained on drug treatment and in the study. Additionally, four patients on acetaminophen 3900 mg/d, two patients on acetaminophen 1950 mg/d, and two patients on placebo had minor transient increases in ALT and/or AST between 1.5 and three times the ULRR. None demonstrated progressive increases in liver function tests.

Discussion

This study demonstrated that acetaminophen ER 3900 mg/d administered for up to 12 weeks was superior to placebo for all three primary end points (WOMAC pain score, WOMAC physical function score, and patient global assessment of response to therapy), as well as for the secondary end point of WOMAC total index. Significant differences were noted at every time point after week 2 and continued through week 12. Acetaminophen ER 1950 mg/d was superior to placebo with respect to patient global assessment of response to therapy. All study treatments were well tolerated, and the overall incidence of adverse events was similar among treatment groups.

Serum transaminase elevations have been observed in other clinical studies conducted with acetaminophen[16–18]. The few elevations that were >3 times the ULRR in this study did not result in serious complications, similar to other published studies[16–18]. In this trial, as in others, comorbid diseases or concomitant medications may have caused elevations in liver function tests.

This study is the first published clinical trial showing the superiority of an ER formulation of acetaminophen over placebo. These results are consistent with the ACR guidelines for treatment of OA, which recommend the use of acetaminophen as first-line therapy for the treatment of OA pain of the hip or knee.

The study has some limitations. Because the purpose was to determine the effective dose of a formulation of acetaminophen not previously evaluated for hip or knee OA and not to compare the formulation to other treatments, a placebo arm was used instead of an active control arm, such as an NSAID. Similarly, statistical comparisons between the two acetaminophen groups were not conducted because the purpose was to determine the least effective dose of acetaminophen. The inclusion criteria required patients to have had a prior response to acetaminophen. An unselected population assuredly would not have had as good a response to acetaminophen, thus it would have been difficult to determine whether the formulation was effective. The study was successful because it showed that the lower dose was not as effective as the higher dose. The authors feel that requiring a prior response to acetaminophen is analogous to the ''flare'' design used in trials of most antiinflammatory agents.

Although there are limited data available on the long-term use of acetaminophen ER and on the efficacy and safety of acetaminophen ER in comparison with an NSAID, data are available for IR acetaminophen demonstrating that it is as effective as NSAIDs[10,11,18,19]. In a randomized, double-blind, clinical trial of 184 patients with chronic knee pain caused by OA, the efficacy of acetaminophen 4000 mg/d was demonstrated to be equivalent to that of either ibuprofen 1200 or 2400 mg/d in the short-term treatment of OA[10]. Williams and colleagues also demonstrated in a randomized, double-blind, clinical trial equal analgesic efficacy and safety between acetaminophen 2600 mg/d and naproxen 750 mg/d in the treatment of OA of the knee[11]. Of note, recently published trial results also provided data on the efficacy and safety of acetaminophen. A multicenter, randomized, double-blind, parallel-group study of patients with OA of the knee or hip demonstrated that sustained regular use of acetaminophen for up to 12 months at recommended doses of 4000 mg/d reduced WOMAC pain, stiffness, and physical function scores to an extent similar to that of naproxen 750 mg/d without evidence of clinically important adverse effects[18].

The current study demonstrates the superiority of acetaminophen over placebo and is consistent with a previous study performed by Amadio and Cummings[19], which concluded that patients taking acetaminophen 4000 mg/d had significant improvement in symptoms (e.g., tenderness, pain at rest, and pain on motion) during a 6-week period as compared with patients receiving placebo.

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